UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte TOSHIAKI TAGAWA and SAIKO HOSOKAWA

Appeal 2007-1079
Application 09/926,358
Technology Center 1600

Decided: April 23, 2007

Before TONI R. SCHEINER, DEMETRA J. MILLS, and ERIC GRIMES, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to liposomes, a cancer medicament comprising them, and a cancer treatment method. The Examiner has rejected the claims for anticipation, obviousness, and obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b). We affirm the obviousness and double-patenting rejections.

BACKGROUND

The Specification describes liposomes comprising maleimidated lipids having a polyalkylene glycol moiety and a GAH antibody "bonded through thioether groups to [the] liposome" (Spec. 4). The Specification states that these liposomes can be used in the treatment of cancer (*id.*).

DISCUSSION

1. CLAIMS

Claims 16-23, 32-34, and 37 are pending and on appeal. The Appeal Brief purports to argue each of the claims separately. However, each of the arguments for separate patentability merely indicates that the applied reference "does not teach" or "does not teach or suggest" "the combination of features as recited" in that claim and points out what that claim additionally recites (see, for example, Br. 17-18 and 27). Appellants provide no reasoned basis for their assertion that the applied references do not teach or suggest the feature recited in that claim. Thus, Appellants' arguments amount to a "statement which merely points out what a claim recites," which is not considered "an argument for separate patentability of the claim." 37 C.F.R. § 41.37(c)(1)(vii). Therefore, the claims subject to each rejection stand or fall together. *Id.*

We will focus on claim 16, the broadest claim on appeal, which reads as follows:

16. A liposome comprising a bonded compound containing a polyalkylene glycol moiety bound to the liposome through thioether groups and a separately bonded antibody bound to the liposome through thioether groups, said liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount

of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome, and said antibody comprising a GAH antibody.

Thus, claim 16 is directed to a liposome whose "partial component has maleimidated terminal." Bonded to the liposome through thioether groups is a 15-30 mole% polyalkylene glycol-containing compound based on one mole of the maleimidated lipid and 1.2-2 mg of antibody, which includes a GAH antibody, per 100 mg of total lipid.

2. PRIOR ART

The Examiner relies on the following references:

Tagawa	US 5,264,221	Nov. 23, 1993
Hosokawa (Hosokawa '869)	US 6,139,869	Oct. 31, 2000
Hosokawa (Hosokawa '153)	US 6,787,153	Sep. 7, 2004

Kirpotin et al., "Sterically stabilized anti-HER2 immunoliposomes: design and targeting to human breast cancer cells *in vitro*," *Biochemistry*, Vol. 36, pp. 66-75 (1997)

3. ANTICIPATION

Claims 16-23 and 32-34 stand rejected under 35 U.S.C. § 102(b) as anticipated by Tagawa. The Examiner relies on Tagawa for disclosing "liposomal compositions wherein the liposomes have maleimide residues on the surface" and a "protein (monoclonal antibody, GAH) and residues of a compound having polyalkylene glycol moiety are bonded via respective groups to the maleimide residues" (Answer 3-4). The Examiner argues that the "mol. percent of the bonded compound as disclosed in the reference on col. 4, lines 59-68 appear[s] to fall within the claimed range" (*id.* at 4).

At column 4, lines 59-68, Tagawa states that "the thiol-modified antibody is employed in an amount of from 0.1% mol to 20% mol per mol of maleimide groups." The Examiner states that Appellants admitted in their August 8, 2005, response (page 9) "that 0.1 mole to 20 mol % of antibody in Tagawa 221 corresponds to 0.3 mg to 60 mg" (Answer 4). The Examiner argues that, although "this is a broad range, . . . in the example, . . . Tagawa 221 uses 5 mg antibody which is . . . not far away from 1.2 to 2 mg" (*id.* at 4-5).

Appellants argue that Tagawa does not teach that the amount of antibody bonded to the liposome is 1.2-2 mg per 100 mg of total lipids (Br. 9-11). We agree that the Examiner has not set forth a prima facie case of anticipation.

In particular, we do not agree that a range of from 1.2-2 mg of antibody per 100 mg of lipid is anticipated by disclosure of a range of 0.3-60 mg of antibody per 100 mg of lipid coupled with an example of 5 mg of antibody per 100 mg lipid. The broad range of 0.3 to 60 does not disclose the narrow range of 1.2 to 2 recited in claim 16 with sufficient specificity to anticipate this range. *See Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006) (reference range of 100-500°C did not describe claimed range of 330-450°C with "sufficient specificity" to anticipate). In addition, a teaching of 5 mg, which is not within the claimed range, does not make up for the lack of specificity. We therefore reverse the rejection of claims 16-23 and 32-34 under 35 U.S.C. § 102.

4. OBVIOUSNESS OVER TAGAWA

Claims 16-23, 32-34, and 37 stand rejected under 35 U.S.C. § 103 as obvious over Tagawa. As discussed above, the Examiner relies on Tagawa for disclosing liposomes comprising maleimidated residues, and monoclonal antibody GAH and a compound having a polyalkylene glycol moiety "bonded via respective groups to the maleimide residues" (Answer 3-4). The Examiner argues that "Tagawa teaches . . . reacting first with the thiol activated antibody and then blocking the remaining maleimide groups on the liposomes with excess amount of thiol modified PEG. Furthermore, in Example 2 on col. 7, Tagawa uses 5 mg of Fb' [sic, Fab'] per hundred mg of lipid" (*id.* at 7.) The Examiner argues that it would have been obvious "to manipulate the amounts of the thiol activated antibody . . . and then block the rest of the maleimide groups on the liposomes with the thiol modified PEG" and that, therefore, the invention of claim 16 is "an obvious extension of [the] prior art's teachings" (*id.*).

We conclude that the Examiner has set forth a prima facie case of obviousness. Tagawa describes "reacting a protein to which a thiol group is imparted (a thiol modified protein) to a liposome having maleimide groups and then reacting a compound having a moiety of a polyalkylene glycol to which a thiol group is imparted (a thiol-modified polyalkylene glycol) to the remaining maleimide groups" (Tagawa, col. 2, ll. 6-11). The protein is preferably an antibody (*id.* at col. 3, ll. 40-44). As the antibody, Tagawa discloses GAH (*id.* at col. 2, ll. 36-40).

Tagawa discloses that "the thiol-modified antibody is employed in an amount of from 0.1% mol to 20% mol per mol of maleimide groups" and

that, "to the remaining maleimide groups, an excess amount of the thiol-modified polyalkylene glycol . . . is added to obtain an antibody-bonded polyalkylene glycol-modified liposome" (*id.* at col. 4, ll. 53-62). In discussing the Japanese counterpart of Tagawa, Appellants indicate that 0.1 to 20 mole% of thiolated antibody per mole of maleimide groups "correspond[s] to 0.3 to 60 mg per 100 mg of the total lipids" (Spec. 2). The range disclosed in Tagawa encompasses the range recited in the claims, and therefore we agree with the Examiner that the claimed liposomes would have been obvious based on the teachings of Tagawa.

Appellants argue that there would have been no motivation to modify the teachings of Tagawa "to provide a liposome, including amongst other features recited in the claim, an amount of the bonded compound [that] is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody [that] is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome" (Br. 25). Appellants argue that Tagawa, by contrast, "discloses the use of a thiolated antibody in a ratio of 0.1 mol% to 20 mol% based on 1 mol of maleimide group" and, in Example 2, "the use of 5 mg antibody per 100 mg of lipids" (Br. 9 (emphasis omitted)). Appellants also argue that Tagawa fails to disclose 15 to 30 mol% polyalkylene glycol moiety "in combination with the specified amount of antibody" (Br. 11). In particular, Appellants argue that, in Tagawa's examples, the amount of bound polyethylene glycol is 47 mol% per one mole of maleimidated lipids (Br. 13, 15; Reply Br. 2).

We are not persuaded by these arguments. As discussed above, Tagawa discloses a broad range of the amount of antibody. Specifically,

Tagawa discloses employing the thiol-modified antibody in amounts corresponding to 0.3 to 60 mg per 100 mg of total lipid, by Appellants' calculations (Spec. 2). Tagawa's range therefore encompasses the range of 1.2 to 2 mg per 100 mg of total lipids recited in claim 16. "[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004). Therefore, we agree with the Examiner that a liposome having 1.2 to 2 mg bound antibody per 100 mg of total lipids would have been obvious based on the teachings of Tagawa.

According to Appellants, Tagawa exemplifies a liposome having 47 mol% bound polyethylene glycol per one mole of maleimidated lipids. Appellants do not describe how this number was derived from Tagawa's examples, but even assuming that it is accurate, we do not agree that this is sufficient to overcome the Examiner's prima facie case that it would have been obvious to have 15 to 30 mole% polyalkylene glycol-containing compound based on one mole of the maleimidated lipid.

Tagawa discloses adding an excess amount of thiol-modified polyalkylene glycol to block excess remaining maleimide groups (Tagawa, col. 4, ll. 62-68). Thus, the amount of bound polyalkylene glycol depends on the amount of available maleimide groups. Even assuming that Tagawa exemplifies a liposome having 47 mol% bound polyethylene glycol per one mole of maleimidated lipids, we agree that one of ordinary skill in the art would have found it obvious to form liposomes having different amounts of polyalkylene glycol-containing compound, including a liposome having 15

to 30 mole% polyalkylene glycol-containing compound based on one mole of the maleimidated lipid. "[I]t is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Appellants also argue that they "have show[n] unexpected results for the claimed subject matter" (Br. 25). In particular, Appellants argue that:

> the unexpected advantages of using a smaller amount of bound antibody . . . is apparent from a review of Appellants' Example 4. As explained in Example 4, a smaller amount of bound antibody gives a higher therapeutic effect, and this result is unexpected by one of ordinary skill in the art in view of Tagawa '221 which discloses the use of a larger amount of bound antibody than the presently claimed liposome.

(*Id.* at 26.)

We are not persuaded by this argument. As shown in Figure 3 of the present application, administering liposomes having 1.2 or 2.0 mg per 100 mg lipids did appear to result in a lower rate of tumor proliferation than for the other liposomes administered in Example 4. Appellants argue that "this result in unexpected" (Br. 26; Reply Br. 4), but have not presented any evidence to support this argument. "[B]y definition, any superior property must be *unexpected* to be considered evidence of non-obviousness. Thus, in order to properly evaluate whether a superior property was unexpected, the [fact-finder] should have considered what properties were expected." *Pfizer, Inc. v. Apotex, Inc.*, __ F.3d __, __, 2007 WL 851203 (Fed. Cir. March 22, 2007). Since Appellants have not shown that the results they rely on were unexpected, they have not provided sufficient evidence to overcome the Examiner's prima facie case of obviousness.

We conclude that the Examiner has set forth a prima facie case that claim 16 would have been obvious over Tagawa, which Appellants have not rebutted. We therefore affirm the rejection of claim 16 under 35 U.S.C. § 103. Claims 17-23, 32-34, and 37 fall with claim 16.

5. OBVIOUSNESS OVER KIRPOTIN AND TAGAWA

Claims 16-23, 32-34, and 37 stand rejected under 35 U.S.C. § 103 as obvious over Kirpotin in combination with Tagawa. We have already concluded that the Examiner has set forth a prima facie case of obviousness for claim 16 based on Tagawa alone, and that Appellants have not overcome this prima facie case. For the same reasons, we affirm the rejection of claim 16 under 35 U.S.C. § 103 as obvious over Kirpotin in combination with Tagawa. Claims 17-23, 32-34, and 37 fall with claim 16.

6. OBVIOUSNESS OVER HOSOKAWA

Claims 16-23, 32-34, and 37 stand rejected under 35 U.S.C. § 103 as obvious over Hosokawa '153 or Hosokawa '869. The Examiner relies on Hosokawa '153 and '869 for disclosing "liposomal compositions wherein the liposomes have maleimide residues on the surface" and a "protein (monoclonal antibody, GAH[)] and residues of a compound having polyalkylene glycol moiety are bonded via respective groups to the maleimide residues" (Answer 12). The Examiner argues that, "[s]ince the examples indicate the amounts of the components in terms of mg, it is unclear whether they correspond to the claimed molar amounts," but that, "[a]ssuming that they are different, it is deemed obvious to one of ordinary skill in the art to vary the amounts to obtain the best possible results" (*id.*). The Examiner also points to Appellants' statement (Br. 44) that "Hosokawa

'153 and Hosokawa '869 . . . disclose the same amount of antibody and the same amount of PEG as Tagawa '221" (Answer 12).

We conclude that the Examiner has set forth a prima facie case of obviousness. Hosokawa '153 and '869 both disclose a human monoclonal antibody, designated GAH, which is "specific to an antigen existing on the surface of a cancer cell membrane" (Hosokawa '153, col. 2, ll. 14-17 and Examples 1-7; Hosokawa '869, col. 2, ll. 13-16 and Examples 1-7). Hosokawa '153 and '869 also disclose binding a monoclonal antibody to the surface of a liposome by reacting a thiolated antibody "with a liposome comprising a lipid into which a maleimide group has been incorporated" and that "[r]emaining maleimide groups on the surface of the liposome may be further reacted with a compound containing thiolated polyalkyleneglycol moiety" (Hosokawa '153 and '869, col. 5, ll. 14-24). In Example 7, Hosokawa '153 and '869 both disclose a liposome having 5 mg antibody per 100 mg lipid (Hosokawa '153 and '869, col. 16, ll. 14-16). For the reasons discussed with regard to Tagawa, we conclude that it would have been obvious to include the amounts of polyalkylene glycol-containing compound and antibody recited in claim 16.

Appellants argue that "the presently claimed liposomes have unexpectedly high suppressive effect against tumor proliferation and superior retention in blood as compared with the liposome with 5 mg antibody per 100 mg lipids" (Br. 44). Appellants also incorporate the arguments set forth earlier in the Appeal Brief (*id.*). For the reasons discussed above, we are not persuaded by these arguments.

We conclude that the Examiner has set forth a prima facie case that claim 16 would have been obvious over Hosokawa '153 or '869, which Appellants have not rebutted. We therefore affirm the rejection of claim 16 under 35 U.S.C. § 103. Claims 17-23, 32-34, and 37 fall with claim 16.

7. DOUBLE PATENTING

Claims 16-23, 32-34, and 37 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-20 of Hosokawa '153 or claims 1-12 of Hosokawa '869. The Examiner states that "the claims in both patented case[s] and [the] instant application are drawn to liposome compositions wherein both an antibody and PEG are attached to the liposome surface through maleimidated terminals of the lipid moiety," that the "[i]nstant claims are generic with respect to the antibody GAH whereas the patented claims are drawn to the antibody fragment of GAH," and that the "patented claims are generic with respect to the amounts of the antibody per 100 mg of lipid" (Answer 13-14). However, the Examiner argues that it "would have been obvious to one of ordinary skill in the art that the GAH antibody would behave the same way as the GAH antibody fraction since it contains said antibody fraction" and that "[a]mounts are deemed to be obvious manipulatable parameters" (*id.* at 13-15).

We conclude that the Examiner has set forth a prima facie case of obviousness-type double patenting. Hosokawa '153 and '869 each claims a pharmaceutical composition comprising a monoclonal antibody fragment (or a monoclonal antibody in Hosokawa '869) bound to the surface of a liposome, wherein "poly(ethylene glycol) is bound to the surface of the liposome through a maleimide group" (Hosokawa '153 and '869, claim 1).

Appellants do not dispute that a GAH antibody would have been obvious, or that it would have been obvious to bond the antibody and the poly(ethylene glycol) to the liposome though thioether groups.

Appellants argue that, even if the entire disclosures of Hosokawa '153 and '869 are used, the rejections are without proper basis for the reasons discussed in the obviousness rejections over these references (Br. 52-53). For the reasons discussed above, we are not persuaded by this argument.

We conclude that the Examiner has set forth a prima facie case that claim 16 is not patentably distinct from the claims of Hosokawa '153 or '869, which Appellants have not rebutted. We therefore affirm the rejection of claim 16 under the judicially created doctrine of obviousness-type double patenting. Claims 17-23, 32-34, and 37 fall with claim 16.

SUMMARY

We affirm the rejections of claims 16-23, 32-34, and 37 under 35 U.S.C. § 103 and under the judicially created doctrine of obviousness-type double patenting. However, we reverse the rejection of claims 16-23 and 32-34 under 35 U.S.C. § 102.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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